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CLINICAL PRACTICE GUIDELINES

Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Incidence and epidemiology

Primary cutaneous lymphomas (PCLs) are defined as non-Hodgkin lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. After gastrointestinal lymphomas, PCLs are the second most common group of extranodal non-Hodgkin lymphomas, with an estimated annual incidence of 1/100 000 in Western countries. PCLs must be distinguished from nodal or systemic malignant lymphomas involving the skin secondarily, which often have another clinical behaviour, have a different prognosis and require a different therapeutic approach. In recent lymphoma classifications, PCLs are therefore included as separate entities. Within the group of PCLs, distinct types of cutaneous T cell lymphoma (CTCL) and cutaneous B cell lymphoma (CBCL) can be distinguished [1, 2]. In the Western world, CTCLs constitute ∼75%–80% of all PCLs [with mycosis fungoides (MF) as the most common type of CTCL] and CBCL ∼20%–25% [1]. However, different distributions have been observed in other parts of the world. In Southeast Asian countries, CTCLs other than MF [in particular Epstein–Barr virus-associated natural killer (NK)/T cell lymphomas] are much more common than in Western countries, while CBCLs are much more uncommon [3, 4]. PCLs are rare diseases and patients should ideally be seen by a multidisciplinary team of dermatologists, pathologists, haematologists and radiation oncologists.

Diagnosis and pathology/molecular biology

The diagnosis and classification of PCLs should always be based on a combination of clinical, histological, immunophenotypical and genetic data. Demonstration of clonal T cell receptor or immunoglobulin gene rearrangements in lesional skin or peripheral blood may be a valuable adjunct in selected cases. However, clinical and histopathological features are, in most cases, the most important deciding factors for therapeutic planning. PCLs should be classified according to the criteria of the revised 2017 World Health Organization (WHO) classification (see Table 1) [2].

Staging and risk assessment

In all cases, adequate staging should be carried out to exclude the presence of extracutaneous disease. Recommendations for the initial staging of patients with MF/Sézary syndrome (SS) are presented in Table 2. Flow cytometry of the peripheral blood is usually recommended for all stages of MF. However, it is debatable whether this test is justified in patients who are not suspected to have SS. Computed tomography (CT) and/or fluorodeoxyglucose-positron emission tomography (FDG-PET) scans are optional in early-stage MF. Bone marrow examination is usually not indicated in patients with MF/SS.

Initial work-up for patients with a PCL other than MF/SS also includes complete physical examination, representative skin biopsy, complete and differential blood cell count, routine serum biochemistry with lactate dehydrogenase (LDH) and appropriate imaging studies (CT and/or FDG-PET scans) [5]. In PCLs with a predominantly subcutaneous presentation, such as subcutaneous panniculitis-like T cell lymphoma (SPTCL) and primary cutaneous gamma/delta T cell lymphoma (PCGD-TCL), FDG-PET is essential to evaluate the extent of disease. In patients with typical lymphomatoid papulosis (LyP) or primary cutaneous $CD4^+$ small/medium T cell lymphoproliferative disorder (LPD), CT and FDG-PET scans are not required. Bone marrow biopsy and

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Table 1. WHO-EORTC classification for cutaneous lymphomas

Cutaneous T cell lymphoma
Mycosis fungoides (MF)
Variants of MF
- Folliculotropic MF
- Pagetoid reticulosis
- Granulomatous slack skin

Sézary syndrome
Primary cutaneous $CD30^+$ lymphoproliferative disorders
- Primary cutaneous anaplastic large cell lymphoma
- Lymphomatoid papulosis

Subcutaneous panniculitis-like T cell lymphoma
Extranodal NK/T cell lymphoma, nasal-type
Primary cutaneous peripheral T cell lymphoma-not otherwise specified
- Primary cutaneous γ/δ T cell lymphoma
- Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T cell lymphoma[a]
- Primary cutaneous acral $CD8^+$ T cell lymphoma[b]
- Primary cutaneous $CD4^+$ small/medium T cell lymphoproliferative disorder[a]

Cutaneous B cell lymphoma
Primary cutaneous marginal zone lymphoma
Primary cutaneous follicle centre lymphoma
Primary cutaneous diffuse large B cell lymphoma, leg type

[a]Provisional entities.
[b]New provisional entity in the revised 2017 WHO classification [2].
EORTC, European Organization of Research and Treatment of Cancer; NK, natural killer; WHO, World Health Organization.
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Table 2. Recommendations for staging evaluation in patients with MF/SS [6]

Complete physical examination including:
- Determination of type(s) of skin lesions
- Identification of any palpable lymph node, especially those ≥ 1.5 cm in largest diameter or firm, irregular, clustered or fixed
- Identification of any organomegaly

Skin biopsy
- Most indurated area if only one biopsy
- Routine histology and immunophenotyping
- Evaluation for clonality of *TCR* gene rearrangement (optional)

Blood tests
- CBC with manual differential, liver function tests, LDH, comprehensive chemistries
- *TCR* gene rearrangement and relatedness to any clone in skin (optional)
- Analysis for abnormal lymphocytes by either Sézary cell count with determination absolute number of Sézary cells and/or flow cytometry (including $CD4^+/CD7^-$ or $CD4^+/CD26^-$) (optional)

Radiological tests
- CT scans of chest, abdomen and pelvis alone ± FDG-PET (optional in patients with early-stage MF)

Lymph node biopsy
- Excisional biopsy in patients with a node that is either ≥ 1.5 cm in diameter and/or is firm, irregular, clustered or fixed
- Routine histology, immunohistochemistry and *TCR* gene rearrangement analysis

CBC, complete blood count; CT, computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; LDH, lactate dehydrogenase; MF, mycosis fungoides; SS, Sézary syndrome; TCR, T cell receptor
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aspirate should be carried out in cutaneous lymphomas with an intermediate or aggressive clinical behaviour but is not required in cutaneous lymphomas with an indolent clinical behaviour, unless indicated by other staging assessments [5, 6]. Bone marrow examination is not indicated in patients with primary cutaneous marginal zone lymphoma (PCMZL), but its significance in primary cutaneous follicle centre lymphomas (PCFCLs) is controversial [5, 7].

Prognosis is extremely variable depending on the type of PCLs and the stage of disease. For clinical staging of MF and SS, the revised tumour, node, metastasis and blood (TNMB) staging system should be used (Tables 3 and 4) [6]. Apart from clinical stage, older age, large cell transformation and increased LDH values have been identified as independent unfavourable prognostic factors in MF [8–10]. For PCLs other than MF/SS, a separate TNM classification system has been published [5]. This staging system is primarily meant to document extent of disease and cannot be used as a prognostic guide.

Treatment

The choice of treatment depends on the type of PCL and the stage of disease. Due to their heterogeneity and rarity, controlled clinical trials in PCLs are almost non-existent, with a few exceptions mainly concerning recently marketed drugs. Recommendations are therefore largely based on (retrospective) cohort studies and expert opinions discussed during consensus meetings of the European Organization of Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Group, the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC) and the International Lymphoma Radiation Oncology Group (ILROG), including consensus recommendations for clinical end points and response criteria in MF/SS [11].

Mycosis fungoides and variants

Since early aggressive chemotherapy (ChT) is associated with considerable side effects but does not improve survival, a stage-adapted conservative therapeutic approach is recommended for MF and its variants [12–15]. Patients with only patches and/or plaques covering < 10% (stage IA) or ≥ 10% of the skin surface (stage IB) should be treated with skin-directed therapies, including topical steroids, psoralens plus ultraviolet A (PUVA), narrow-band ultraviolet B (nb-UVB) and topical cytostatic agents, such as mechlorethamine (nitrogen mustard) (Figure 1). nb-UVB is recommended for patients with patches or very thin plaques but PUVA is preferred for patients with thicker plaques [III, A] [13, 15]. Topical steroids can be recommended as monotherapy for stage IA disease with patches/flat plaques. In stage IB,

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Table 3. Revised TNMB classification of MF/SS [6]

T (skin)	
T1	Limited patch/plaque (involving < 10% of total skin surface)
T2	Generalised patch/plaque (involving ≥ 10% of total skin surface)
T3	Tumour(s)
T4	Erythroderma
N (lymph node)	
N0	No clinically abnormal peripheral lymph nodes
N1	Clinically abnormal peripheral lymph nodes; histologically uninvolved
N2	Clinically abnormal peripheral lymph nodes; histologically involved (nodal architecture uneffaced)
N3	Clinically abnormal peripheral lymph nodes; histologically involved [nodal architecture (partially) effaced]
Nx	Clinically abnormal peripheral lymph nodes; no histological confirmation
M (viscera)	
M0	No visceral involvement
M1	Visceral involvement
B (blood)	
B0	No circulating atypical (Sézary) cells (or < 5% of lymphocytes)
B1	Low blood tumour burden (≥ 5% of lymphocytes are Sézary cells, but not B2)
B2	High blood tumour burden (≥ 1000/μl Sézary cells and positive clone)

MF, mycosis fungoides; SS, Sézary syndrome; TNMB, tumour, node, metastasis, blood.

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Table 4. Revised clinical staging system for MF/SS [6]

Clinical stage				
IA	T1	N0	M0	B0-1
IB	T2	N0	M0	B0-1
IIA	T1–2	N1-2	M0	B0-1
IIB	T3	N0–2	M0	B0-1
III	T4	N0–2	M0	B0-1
IVA1	T1–4	N0-2	M0	B2
IVA2	T1–4	N3	M0	B0-2
IVB	T1–4	N0–3	M1	B0-2

MF, mycosis fungoides; SS, Sézary syndrome.

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topical steroids can be used as adjuvant therapy for selected skin lesions. Topical application of mechlorethamine, either in aqueous solution or in an ointment-based preparation, has been used successfully for decades in the treatment of early-stage MF. A commercial 0.02% gel preparation was approved by the European Medicines Agency (EMA) as an orphan drug for the treatment of early stage MF [II, B] [16]. In patients developing one or few infiltrated plaques or tumours (stage IIB), additional low-dose local radiotherapy (RT) may suffice [III, A] [17]. Local RT can be curative in patients with early localised disease, particularly in patients with unilesional MF and pagetoid reticulosis [IV, A]. In such patients, local RT is most commonly administered with electrons (energy dependent on the thickness of the lesion), with bolus to achieve full skin dose, a margin of ≥ 2 cm and a total dose of 20–24 Gy [IV, A] [18]. For patients with more extensive infiltrated plaques and tumours, or patients refractory to skin-directed therapies, systemic therapy with interferon alpha (IFNα) or retinoids (including bexarotene), commonly combined with PUVA or other skin-directed therapies, or a combination of IFNα and retinoids or total skin electron beam therapy (TSEBT), can be considered [III, B] [13, 15, 19]. TSEBT was often given to total doses of 30–36 Gy, but lower doses (10–12 Gy) have been employed with the advantages of shorter duration of the treatment period, fewer side effects and opportunity for re-treatment [III, A] [20, 21]. In patients with advanced and refractory disease, gemcitabine or liposomal doxorubicin may be considered, but responses are generally short-lived [II, B] [22, 23]. Other agents like the fusion toxin denileukin diftitox and histone deacetylase (HDAC) inhibitors, such as vorinostat and romidepsin, have been approved in the United States by the Food and Drug Administration (FDA) for patients with relapsed and refractory CTCL, but have not yet been registered for CTCL in Europe [24–26]. Multi-agent ChT is only indicated in patients with effaced lymph nodes or visceral involvement (stage IV), or in patients with widespread tumour stage MF, which cannot be controlled with skin-targeted and immunomodulating therapies or who failed single-agent ChT, but—similar to single-agent ChT—responses are generally short-lived [IV, B] [27]. Local palliation of cutaneous as well as extracutaneous lesions may be achieved with local RT to doses ≥ 8 Gy [III, A] [17].

Recent studies report high response rates of brentuximab vedotin (BV; an anti-CD30 monoclonal antibody coupled to the anti-tubulin agent monomethyl auristatin E) in patients with advanced MF/SS expressing CD30 [II, B] [28–30]. In a phase II trial including 28 patients with $CD30^+$ relapsed or refractory MF, BV showed a 54% overall response rate (ORR) with a median time to response of 12 weeks and a median duration of response of 32 weeks in patients with MF, independent of the degree of CD30 expression [28]. Another phase II study reported an ORR of 70% in a group of 32 patients with relapsed or refractory MF/SS with a wide range of CD30 expression levels [29]. Results from a recent phase III trial, which compared BV to physician's choice of methotrexate (MTX) or bexarotene in 128 patients with relapsed or refractory $CD30^+$ CTCL, including 97 patients with MF, showed ORR lasting at least 4 months (ORR4) and complete response (CR) rate of 50% and 10%, respectively, in MF patients treated with BV compared with 10% and 0%, respectively, in the control group [30]. Median progression-free survival (mPFS) was 15.9 months in the BV group compared with 3.5 months in the control group.

In relatively young patients with refractory, progressive MF or with SS, allogeneic stem cell transplantation (alloSCT) should be considered. Durable responses have been reported, but experience is still limited and the optimal conditioning regimen and the optimal timing for an allogeneic transplant are currently

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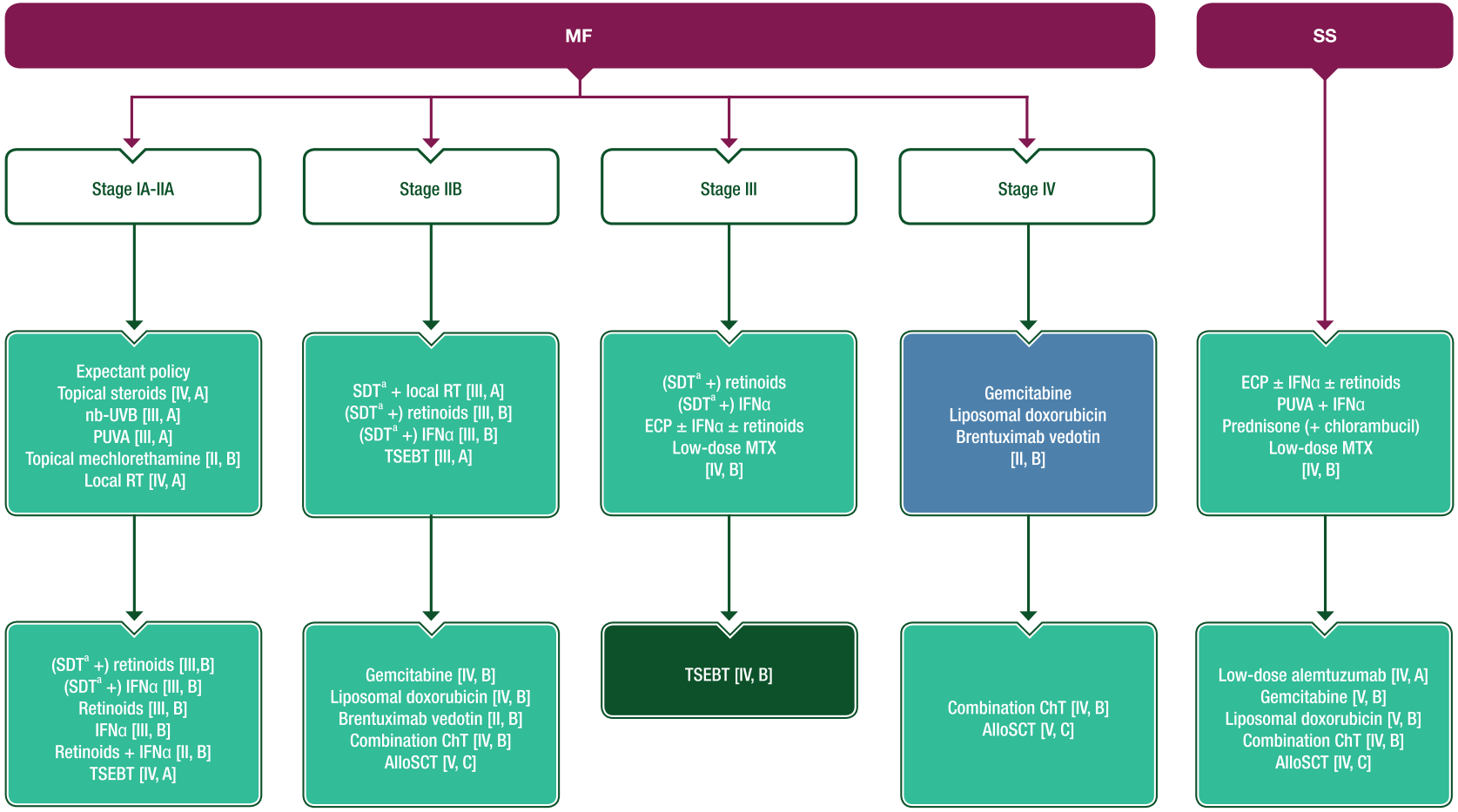

Figure 1. Recommendations for the treatment of MF/SS.

[a]Most commonly PUVA.

AlloSCT, allogeneic stem cell transplantation; ChT, chemotherapy; ECP, extracorporeal photopheresis; IFNα, interferon alpha; MF, mycosis fungoides; MTX, methotrexate; nb-UVB, narrow-band ultraviolet B; PUVA, psoralens plus ultraviolet A; RT, radiotherapy; SS, Sézary syndrome; SDT, skin-directed therapy; TSEBT, total skin electron beam therapy.

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unknown [V, C] [31]. Recent studies suggest that patients may benefit from tumour debulking with TSEBT or BV before transplantation [32, 33]. Results with autologous stem cell transplantation (ASCT) in MF and SS have been disappointing.

Promising new drugs are currently under evaluation in clinical trials, including mogamulizumab [34–36]. A phase I/II open-label multicentre, randomised clinical trial demonstrated an ORR of 47% for SS patients and 29% in MF patients, with a dramatic clearance of malignant cells from the peripheral blood in 18 of 19 patients with blood involvement [35]. An open-label multicentre randomised phase III study comparing mogamulizumab with vorinostat in 372 patients with relapsed or refractory MF or SS showed a significantly better ORR (28% versus 5%) and PFS (7.7 months versus 3.1 months) in the mogamulizumab group [36].

Sézary syndrome

SS is defined by a triad of erythroderma, generalised lymphadenopathy and the presence of clonally related neoplastic T cells with cerebriform nuclei (Sézary cells) in skin, lymph nodes and peripheral blood [1, 2]. Being a systemic disease (i.e. leukaemia) by definition, systemic treatment is required (Figure 1). Skin-directed therapies like PUVA or potent topical steroids may be used as adjuvant therapy. Extracorporeal photopheresis (ECP), either alone or in combination with other treatment modalities such as IFNα, retinoids, TSEBT and PUVA, has been suggested as the treatment of choice in SS and erythrodermic MF [IV, B] [13–15]. ORRs range from 30% to 80% with CR rates ranging from 14% to 25%, depending on the ECP regimen and the type of combination used. However, the suggested superiority of ECP over the traditional low-dose ChT regimens has not yet been substantiated by controlled randomised trials [37]. Prolonged treatment with a combination of low-dose chlorambucil and prednisone is often effective in controlling the disease but is unlikely to yield complete responses. Low-dose alemtuzumab (10 mg subcutaneous, 3 times weekly for 12 weeks) [IV, A], single-agent ChT (gemcitabine, PEGylated liposomal doxorubicin) [V, B], multi-agent ChT [IV, B] and alloSCT [IV, C] have been recommended as second-line treatment of SS [13, 15, 38]. It should be emphasised that comparison of treatment results in the different studies is almost impossible due to differences in diagnostic criteria used for SS.

Primary cutaneous CD30$^+$ lymphoproliferative disorders

The group of primary cutaneous CD30$^+$ LPDs includes primary cutaneous anaplastic large cell lymphoma (C-ALCL) and LyP, which form a spectrum of disease. Both C-ALCL and LyP have an excellent prognosis, with a 10-year survival of 90% and almost 100%, respectively [39]. LyP is clinically characterised by recurrent, self-healing papulonecrotic or papulonodular skin lesions. Since a curative therapy is not available and none of the available treatment modalities affects the natural course of the disease, in patients with relatively few non-scarring lesions, an expectant

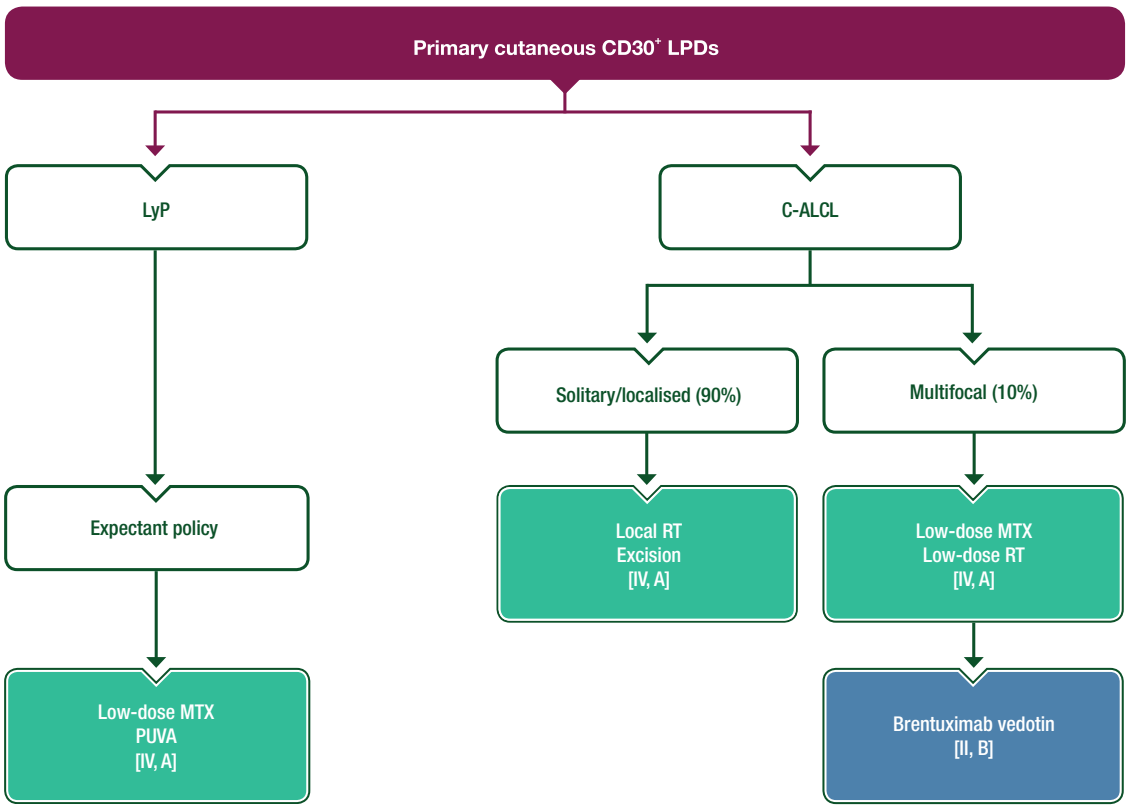

Figure 2. Recommendations for the initial management of primary cutaneous CD30$^+$ LPDs.
C-ALCL, cutaneous anaplastic large cell lymphoma; LPD, lymphoproliferative disorder; LyP, lymphomatoid papulosis; MTX, methotrexate; PUVA, psoralens plus ultraviolet A; RT, radiotherapy.

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policy can be followed (Figure 2). In the case of cosmetically disturbing lesions (e.g. scarring or many papulonodules), low-dose oral MTX (5–20 mg/week) and PUVA are the most effective therapies for reducing the number of skin lesions [IV, A] [39–41]. Relapses after withdrawal of treatment are common and maintenance treatment is often required for adequate disease control. Patients with C-ALCL generally present with solitary or localised (ulcerating) tumours or nodules and should be treated with RT or surgical excision (Figure 2). In case of complete spontaneous remission, no further therapy is required [39]. Patients presenting with multifocal skin lesions can best be treated with low-dose MTX, as in LyP [IV, A], or with RT [IV, A] in the case of only a few lesions [39, 40, 42]. The ILROG suggests radiation with electrons, with bolus, a margin of ≥ 2 cm and a total dose of 24–30 Gy [18, 43]. In a recent study in 63 patients with C-ALCL, a total dose of 20 Gy in 8–10 fractions was found to be effective and well-tolerated in patients presenting with solitary or localised skin lesions. For patients with multifocal or relapsing skin lesions, a radiation dose of 8 Gy (2×4 Gy) was suggested [44].

Recent studies report high response rates of BV in patients with primary cutaneous $CD30^+$ lymphoproliferations [28–30]. In the phase III trial, which compared BV to physician's choice of MTX or bexarotene, BV showed an ORR4 and CR rate of 75% and 31%, respectively, in C-ALCL patients treated with BV compared with 20% and 7%, respectively, in the control group [30]. BV should be considered in cases with multifocal skin lesions refractory to conventional therapies and in patients developing extracutaneous disease [II, B] [42]. Multi-agent ChT is only indicated in patients presenting with or developing extracutaneous disease and in rare patients with rapidly progressive skin disease [39, 40].

Subcutaneous panniculitis-like T cell lymphomas

The term SPTCL is only used for cases with an α/β T cell phenotype, which have a favourable prognosis, particularly if not associated with a haemophagocytic syndrome (HPS), which is frequently an extremely aggressive clinical syndrome requiring immediate intervention. One study reported 5-year overall survival (OS) rates of 91% and 46% in SPTCL patients without and with an HPS, respectively [45]. In SPTCL without associated HPS, systemic steroids or other immunosuppressive agents (ciclosporin, MTX) should be considered first; in cases of solitary skin lesions, RT with electrons is advised [IV, A]. Little information on radiation dose is available, but a dose of 40 Gy has been used. Bexarotene may be also effective in SPTCL [46]. Multi-agent ChT is required only in cases with progressive disease not responding to immunosuppressive therapy and in cases with HPS.

Primary cutaneous extranodal NK/T cell lymphoma, nasal type

Primary cutaneous extranodal NK/T cell lymphoma, nasal type is an Epstein–Barr virus-associated type of lymphoma with an aggressive clinical behaviour, which is very rare in Western countries, but more common in Asia and Central and South America [2]. The skin is the second most common site of involvement after the nasal cavity/nasopharynx and, in some patients, skin lesions may be the only manifestation of disease [47–49]. Patients presenting with only localised skin lesions (stage IE) have a somewhat better prognosis than localised lesions in non-cutaneous sites [48, 49]. In rare cases with small, solitary lesions, RT alone can be considered, as long-term disease control has been achieved with this approach in some reported cases [V, C] [50–52]. This is also the option for older or frail patients who cannot tolerate intensive ChT. In general, however, combined modality treatment with L-asparaginase containing ChT, such as SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) is the preferred mode of treatment, combined with RT, for localised disease, as it is for nasal NK/T cell lymphomas, although there is still a paucity of data on the outcome of this treatment in primary cutaneous NK/T cell lymphoma [V, B] [53]. Recommended radiation doses are higher than for other lymphomas, with 50 Gy to the initial lesion and a boost of 5–10 Gy to residual disease [IV, A] [18]. In patients presenting with generalised skin lesions, the disease shows an aggressive clinical behaviour and should be treated as other patients with stage II–IV disease [53].

Primary cutaneous peripheral T cell lymphoma-not otherwise specified

Within the group of primary cutaneous peripheral T cell lymphoma-not otherwise specified (PTCL-NOS), four somewhat better-defined subgroups have been included as (provisional) entities (see Table 1) [1, 2]. These include PCGD-TCL, primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T cell lymphoma ($CD8^+$ AECTCL), primary cutaneous $CD4^+$ small/medium T cell LPD and primary cutaneous acral $CD8^+$ T cell lymphoma. For cases that do not fit into one of the well-defined types of CTCL, including these rare subtypes, the term primary cutaneous PTCL-NOS is maintained. Both PCGD-TCL and $CD8^+$ AECTCL have in common a generally aggressive clinical course and poor prognosis, and should therefore be managed according to the ESMO guidelines for PTCL-NOS [53]. Patients with primary cutaneous $CD4^+$ small-medium T cell LPD and patients with a primary cutaneous acral $CD8^+$ T cell lymphoma have an indolent clinical behaviour and excellent prognosis. Patients usually present with a solitary skin lesion, which should be treated with local RT or surgical excision [IV, A].

Cutaneous B cell lymphoma

In the WHO-EORTC classification, three main types of CBCL are distinguished: PCMZL, PCFCL and primary cutaneous diffuse large B cell lymphoma, leg type (PCLBCL-LT). PCMZL and PCFCL are indolent types of CBCL with a disease-related 10-year-survival exceeding 90%, while PCLBCL-LT has a more unfavourable prognosis (disease-related 5-year survival, approximately 50%). EORTC/ISCL consensus recommendations for the management of these three types of CBCL have been formulated and are, with minor modifications, presented in Figures 3 and 4 [54]. Recommended radiation doses for localised PCMZL and PCFCL are 24–30 Gy [IV, A], whereas for palliative treatment of multifocal disease, low-dose RT (4 Gy) is often sufficient [III, A] [17, 18]. For the more aggressive PCLBCL-LT, systemic treatment with rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) is recommended if the patient can tolerate multi-agent ChT [IV, A]. For localised disease, the systemic treatment is combined with RT, and a radiation dose of 36–40 Gy is recommended; if no systemic treatment is given, a dose of 40 Gy is recommended [IV, B] [18]. These patients are often elderly, and for disseminated or recurrent disease,

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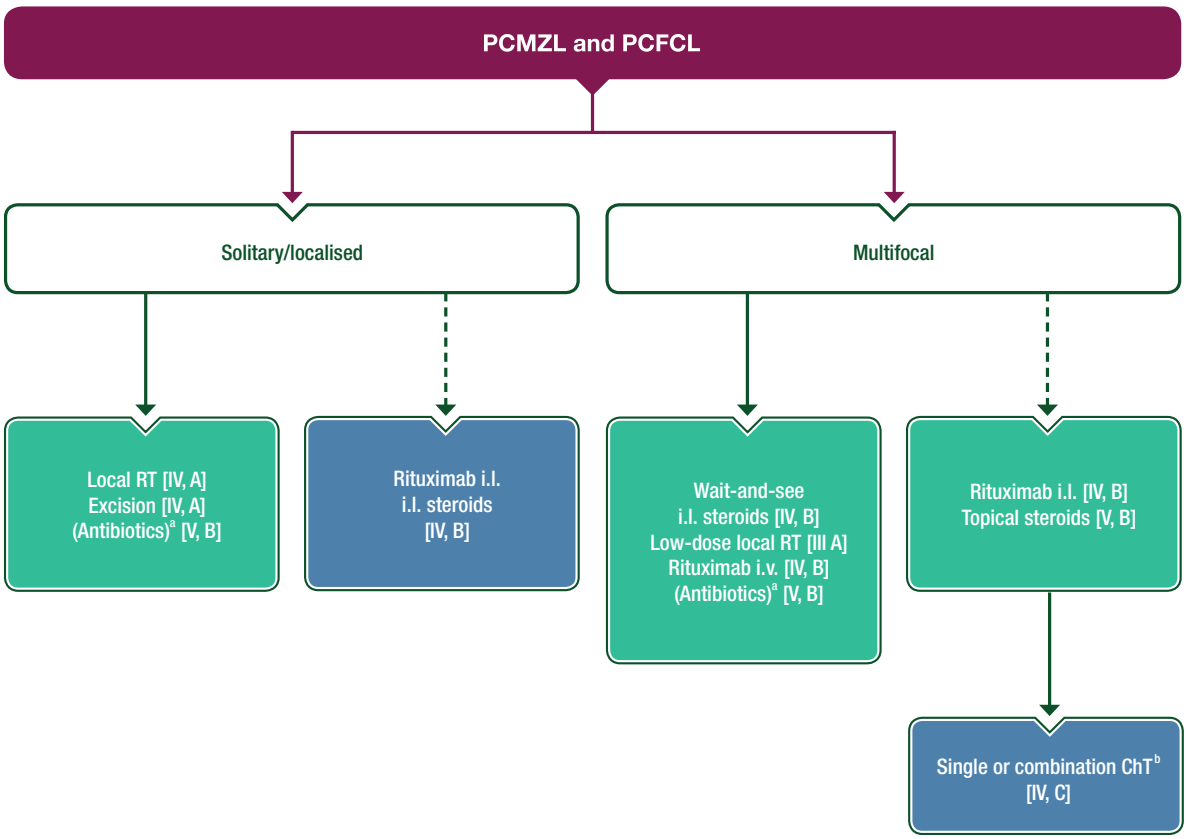

Figure 3. Recommendations for the initial management of PCMZL and PCFCL.
[a]In the case of evidence for *Borrelia burgdorferi* infection.
[b]Single or combination chemotherapy appropriate for low-grade malignant B cell lymphomas.
ChT, chemotherapy; i.l., intralesional; i.v., intravenous; PCFCL, primary cutaneous follicle centre lymphoma; PCMZL, primary cutaneous marginal zone lymphoma; RT, radiotherapy.

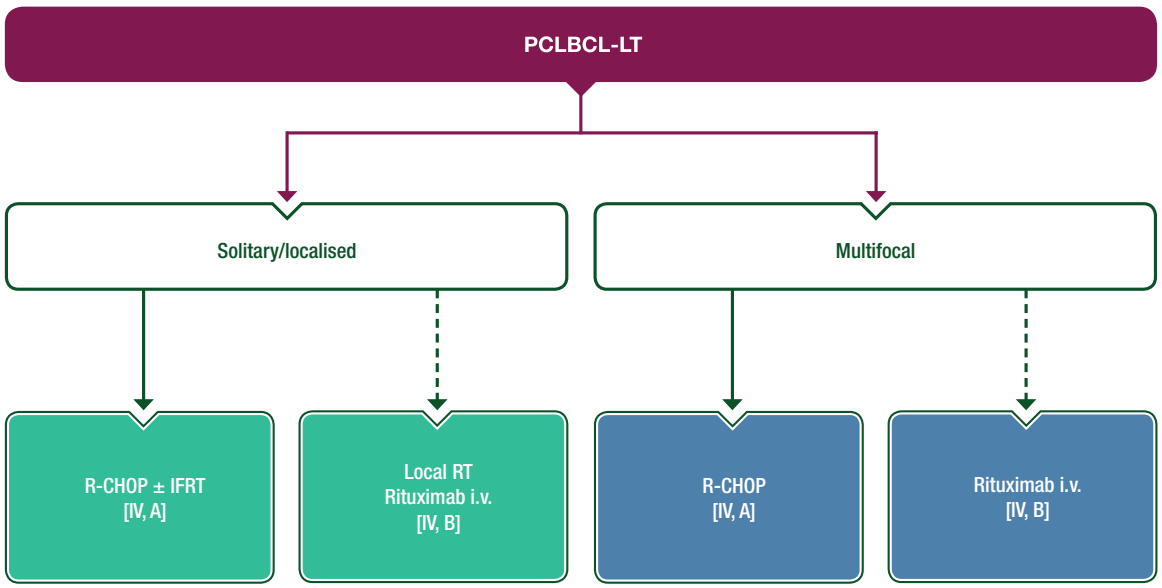

Figure 4. Recommendations for the initial management of PCLBCL-LT.
IFRT, involved-field radiotherapy; i.v., intravenous; PCLBCL-LT, primary cutaneous large B cell lymphoma, leg type; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RT, radiotherapy.

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Table 5. Summary of recommendations

Incidence and epidemiology

- PCLs must be distinguished from nodal or systemic malignant lymphomas involving the skin secondarily. In recent lymphoma classifications, PCLs are included as separate entities

Diagnosis and pathology/molecular biology

- The diagnosis and classification of PCLs should be based on a combination of clinical, histological, immunophenotypical and genetic data

Staging and risk assessment

- Adequate staging should be carried out to exclude the presence of extracutaneous disease
- Initial work-up for patients with a PCL includes complete physical examination, representative skin biopsy, complete and differential blood cell count, routine serum biochemistry with LDH and appropriate imaging studies
- In PCLs with a predominantly subcutaneous presentation (such as SPTCL and PCGD-TCL), FDG-PET is essential to evaluate the extent of disease

Treatment

- The choice of treatment depends on the type of PCL and the stage of disease. Due to their heterogeneity and rarity, controlled clinical trials in PCLs are almost non-existent, with a few exceptions mainly concerning recently marketed drugs
- Recommendations are largely based on (retrospective) cohort studies and expert opinions

Mycosis fungoides and variants

- In MF and its variants, a stage-adapted conservative therapeutic approach is recommended
- Patients with early-stage MF (stage IA–IIA) should be treated with skin-directed therapies including topical steroids, PUVA, nb-UVB or mechlorethamine
- nb-UVB can be used in patients with patches or very thin plaques. In patients with thicker plaques, PUVA therapy is preferred [III, A]
- In patients developing one or few infiltrated plaques or tumours (stage IIB), additional low-dose local RT may suffice [III, A]
- Local RT can be curative in patients with unilesional MF and pagetoid reticulosis [IV, A]. Recommended dose is 20–24 Gy [IV, A]
- For patients with more extensive infiltrated plaques and tumours or patients refractory to skin-directed therapies, a combination of PUVA and IFNα or PUVA and retinoids (including bexarotene), a combination of IFNα and retinoids or TSEBT can be considered [III, B]
- TSEBT has been given to total doses of 30–36 Gy, but recently lower doses (10–12 Gy) have been employed with the advantages of shorter duration of the treatment period, fewer side effects and opportunity for re-treatment [III, A]
- In patients with advanced and refractory disease, gemcitabine or liposomal doxorubicin may be considered, but responses are generally short-lived [II, B]
- Multi-agent ChT is only indicated in MF patients with effaced lymph nodes or visceral involvement (stage IV), or in patients with widespread tumour stage MF, which cannot be controlled with skin-targeted and immunomodulating therapies or who failed single-agent ChT
- Local palliation of cutaneous and as well as extracutaneous lesions may be achieved with local RT to doses $\geq$ 8 Gy [III, A]
- In relatively young patients with refractory, progressive MF alloSCT should be considered. The optimal conditioning regimen and timing for an allogeneic transplant are currently unknown [IV, C]

Sézary syndrome

- Systemic treatment is required in combination with skin-directed therapies like PUVA or potent topical steroids used as adjuvant therapy
- ECP, either alone or in combination with other treatment modalities such as IFNα, retinoids, TSEBT and PUVA, has been suggested as the treatment of choice in SS and erythrodermic MF [IV, B]
- Mogulizumab has shown significant clinical efficacy in MF/SS, particularly in patients with blood involvement
- In relatively young patients with refractory, progressive SS, alloSCT should be considered. The optimal conditioning regimen and timing for an allogeneic transplant are currently unknown [IV, C]
- Low-dose alemtuzumab (10 mg subcutaneous, 3 times weekly for 12 weeks) [IV, A], single-agent ChT (gemcitabine, PEGylated liposomal doxorubicin) [V, B], multi-agent ChT [IV. B] and alloSCT [IV. C] are recommended as second-line treatment of SS.

Primary cutaneous CD30$^+$ lymphoproliferative disorders (C-ALCL and LyP)

- In the case of cosmetically disturbing lesions (e.g. scarring or many papulonodules), low-dose oral MTX (5–20 mg/week) and PUVA are the most effective therapies for reducing the number of skin lesions [IV, A]
- Local RT is the first choice of treatment in patients with C-ALCL presenting with solitary or localised skin lesions. A total dose of 20 Gy is recommended
- C-ALCL patients presenting with multifocal skin lesions can best be treated with low-dose MTX, as in LyP [IV, A], or RT [IV, A] in the case of only a few lesions
- BV should be considered in C-ALCL patients with multifocal skin lesions refractory to conventional therapies and patients developing extracutaneous disease [II, B]
- Multi-agent ChT is only indicated in patients presenting with or developing extracutaneous disease and in rare patients with rapidly progressive skin disease

Subcutaneous panniculitis-like T cell lymphomas

- In SPTCL without associated HPS, systemic steroids or other immunosuppressive agents (ciclosporin; MTX) are the first choice of treatment. In cases of solitary skin lesions, RT with electrons is advised [IV, A]
- Multi-agent ChT is required only in cases with progressive disease not responding to immunosuppressive therapy and in cases with HPS

Primary cutaneous extranodal NK/T cell lymphoma, nasal type

- Primary cutaneous extranodal NK/T cell lymphoma is an aggressive lymphoma. Combined modality treatment with L-asparaginase containing ChT, such as SMILE (dexamethasone, methotrexate, ifosphamide, L-asparaginase, etoposide), combined with RT for patients with localised disease, is the preferred mode of treatment [V, B], In rare cases with small, solitary lesions, and in older or frail patients who cannot tolerate intensive ChT, RT alone can be considered [V, C]

Continued

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Primary cutaneous peripheral T cell lymphoma - not otherwise specified

- PCGD-TCL and primary cutaneous $CD8^+$ AECTCL are aggressive types of CTCL, which should be managed as systemic PTCL-NOS
- Patients with a primary cutaneous $CD4^+$ small-medium T cell LPD or a primary cutaneous acral $CD8^+$ T cell lymphoma usually present with a solitary skin lesion, which should be treated with local RT or surgical excision [IV, A]

Cutaneous B cell lymphoma

- Recommended radiation doses for localised PCMZL and PCFCL are 24-30 Gy [IV, A]. For palliative treatment of multifocal disease, low-dose RT (4 Gy) is often sufficient [IV, A]
- For the more aggressive PCLBCL-LT, systemic treatment with R-CHOP combined with RT at a radiation dose of (36–40 Gy) is recommended for localised disease if the patient can tolerate multi-agent ChT [IV, A]. If no systemic treatment is given, a dose of 40 Gy is recommended [IV, B]
- PCLBCL-LT has the phenotype and gene expression profile of ABC-type DLBCL and should be treated as other ABC-type DLBCLs

Personalised medicine

- BV is used for the treatment of advanced stage refractory or relapsed $CD30^+$ CTCL, including both patients with C-ALCL and patients with MF/SS, also with the purpose of bridging eligible patients with MF/SS to an alloSCT
- PCLBCL-LT shows a high frequency of *MYD88* and *CD79B* mutations
- The efficacy of BTK inhibitors, which targets this pathway, is currently under investigation

Follow-up, long-term implications and survivorship

- Follow-up recommendations should be individualised depending on the clinical situation. The frequency of follow-up visits varies depending on PCL type and the stage of disease from every 6 or 12 months in patients with indolent types of PCL and stable disease or patients in complete remission to every 4–6 weeks in patients with active or progressive disease
- Follow-up visits should focus on history and physical examination, with additional testing only if required. Routine imaging after treatment is not required, since tumour responses are visible to the naked eye and in most instances recurrences are also localised in the skin

ABC, activated B cell; alloSCT, allogeneic stem cell transplantation; BTK, Bruton's tyrosine kinase; BV, brentuximab vedotin; C-ALCL, cutaneous anaplastic large cell lymphoma; $CD8^+$ AECTCL, primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T cell lymphoma; ChT, chemotherapy; CTCL, cutaneous T cell lymphoma; DLBCL, diffuse large B cell lymphoma; ECP, extracorporeal photopheresis; FDG-PET, fluorodeoxyglucose-positron emission tomography; HPS, haemophagocytic syndrome; IFNα, interferon alpha; LDH, lactate dehydrogenase; LPD, lymphoproliferative disorder; LyP, lymphomatoid papulosis; MF, mycosis fungoides; MTX, methotrexate; nb-UVB, narrow-band ultraviolet B; NK, natural killer; PCFCL, primary cutaneous follicle centre lymphoma; PCGD-TCL, primary cutaneous gamma/delta T cell lymphoma; PCL, primary cutaneous lymphoma; PCLBCL-LT, primary cutaneous diffuse large B cell lymphoma, leg type; PCMZL, primary cutaneous marginal zone lymphoma; PTCL-NOS, primary cutaneous peripheral T cell lymphoma-not otherwise specified; PUVA, psoralens plus ultraviolet A; R-CHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RT, radiotherapy; SPTCL, subcutaneous panniculitis-like T cell lymphoma; SS, Sézary syndrome; TSEBT, total skin electron beam therapy.

rituximab as a single drug may achieve remissions. PCLBCL-LT has the phenotype and gene expression profile of ABC-type diffuse large B cell lymphoma (DLBCL) and shows a high frequency of *MYD88* and *CD79B* mutations, which results in constitutive activation of nuclear factor kappa light chain enhancer of activated B cells (NF-κB) signalling [55]. Recent studies suggest that PCLBCL-LT patients may benefit from treatment with Bruton's tyrosine kinase (BTK) inhibitors, which block the NF-κB pathway [56].

Personalised medicine

Personalised approaches in the treatment of PCL are still limited. BV is used for the treatment of advanced stage refractory or relapsed $CD30^+$ CTCL, including both patients with C-ALCL and patients with MF/SS, also with the purpose of bridging eligible patients to an alloSCT [28–30, 33]. Mogamulizumab is a humanised monoclonal antibody targeting the CC chemokine receptor 4 (CCR4), which is overexpressed on the malignant T cells in MF/SS. Mogamulizumab has shown significant clinical efficacy in MF/SS, particularly in patients with blood involvement [34–36]. PCLBCL-LT frequently shows *MYD88* and *CD79B* mutations, resulting in constitutive NF-κB activation [55]. The efficacy of BTK inhibitors that target this pathway is currently under investigation but reports on their efficacy in CBCL are still scarce [56].

Follow-up, long-term implications and survivorship

Follow-up recommendations should be individualised depending on the clinical situation. The frequency of follow-up visits depends on the type of PCL and the stage of disease. It may vary from every 6 or 12 months in patients with indolent types of PCL and stable disease or patients in complete remission to every 4–6 weeks in patients with active or progressive disease. Follow-up visits should focus on history and physical examination, and additional testing (histology, blood examination, imaging, etc.) should only be carried out if required. Routine imaging after treatment is not required, since tumour responses are visible to the naked eye and in most instances, recurrences are also localised in the skin. Survivorship issues are poorly studied in PCLs and are probably similar to those of patients with more common lymphomas with the same prognosis treated similarly. A long-term implication specifically found in PCL patients is the increased risk for developing skin cancers, in particular squamous cell carcinomas, following long-term treatment with PUVA.

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical

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Table 6. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity

II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity

III Prospective cohort studies

IV Retrospective cohort studies or case–control studies

V Studies without control group, case reports, experts opinions

Grades of recommendation

A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended

B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .) optional

D Moderate evidence against efficacy or for adverse outcome, generally not recommended

E Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [57].

Practice Guidelines development, http://http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 5. Levels of evidence and grades of recommendation have been applied using the system shown in Table 6. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Disclosure

RW has reported global advisory boards for Takeda and Actelion; EH has reported advisory boards for Takeda and Actelion; PLZ has reported advisory boards for Kirin Kyowa, Takeda, Verastem, Janssen, Roche, Celgene, Bristol-Myers Squibb and Merck; LS has reported advisory boards for Takeda and Merck and research agreements with Takeda and Varian; ML has reported consultancy, participation to advisory boards and research support from Abbvie, Acerta, Amgen, Archigen, Celgene, ADC Therapeutics, Gilead, Novartis, Johnson & Johnson, Roche, Roche Diagnostics, Sandoz and Takeda.

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